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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,761	03/25/2004	Charles R. Stewart	61683-00004USPT	8658
24238	7590	09/12/2005	EXAMINER	
JENKENS & GILCHRIST 1401 MCKINNEY SUITE 2600 HOUSTON, TX 77010			MAYER, SUZANNE MARIE	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
10/809,761	STEWART ET AL.	
Examiner	Art Unit	
Suzanne M. Mayer, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 June 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-15, 17-20 and 22-28 is/are pending in the application.
- 4a) Of the above claim(s) 26-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-15, 17-20 and 22-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on June 6, 2005 and 3-25-2004 in-part is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3-4-2005</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Election/Restrictions

1. Applicant's argument asserting that a provisional response to the restriction requirement of January 14, 2005 is tantamount to an election that has been made with traverse. Applicants also assert that the election was provisionally made to a Markush-type restriction requirement. The examiner wishes to specifically point out two matters on this subject. The examiner in no uncertain terms, clearly and distinctly pointed out in the restriction requirement from December 16, 2004, that the election of a single sequence was *NOT* an election of species, and therefore Markush-type restriction practice was never asserted or used by the examiner. Applicants suggest that it would not be an undue burden for the examiner to examine all of the sequences claimed because they all come from the same *Bacillus subtilis* SPO1 genome, and thus the 24 genes and 24 proteins should be considered as species. However, this is not persuasive because, as an analogous example of Applicants arguments, the arguments presented suggest Markush-type practice is warranted, for example, for the entire *E. coli* genome and the 4290 proteins from this bacterium could be claimed and be expected to be searched and treated as an election of species solely because they are derived from the same genome. Similarly, the analogy stands for the human genome and the millions of proteins found in humans. Furthermore, applicants failed to specifically point out any deficiencies made in the restriction requirement whatsoever in the election filed January 18, 2005. Thus, pursuant to the MPEP § 818.03(a)), because applicant did not distinctly and specifically point out the supposed errors in the

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restriction requirement, the election has been treated as an election without traverse. In doing so, Applicants have forfeited their rights to further argue the restriction requirement. Therefore, the arguments subsequently made by Applicants regarding the restriction and subsequent election in the remarks filed June 6, 2005 (which was in response to the First Office action) will not be further addressed.

Status of the Claims

2. Claims 11-15, 17-20 and 22-28 drawn to SEQ ID No: 8 are pending in this application. Claim 20 was cancelled by Applicants. Claims 22-28 are newly added claims. Claims 26-28 are withdrawn from further consideration as being drawn to non-elected subject matter. Thus claims 11-15, 17-20 and 22-25 are under examination.

Withdrawn Objections and Rejections

Drawings

3. The objection to the drawings of the previous Office action are withdrawn. The replacement drawings for Figures 5, 9 and 10 June 6, 2005 are accepted by the examiner.

Specification

4. The objection to the specification is hereby withdrawn in view of the amendment removing the embedded hyperlinks.

Claim Rejections - 35 USC § 112

5. Withdrawl of the rejection of claims 11-12, 19 and 21 under 35 USC § 112 1st paragraph, enablement and written description is withdrawn in view of the amendment deleting reference to peptidomimetic small molecules.

Maintained Objections and Rejections

Claim Objections

6. Claims 11, 13-14, 18, 20 and newly added claims 22-23 are objected to because of the following informalities: The claims contain non-elected subject matter.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
8. Claims 11-15 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. The reasonings for the rejection are described in the previous Office action and further explained in the Response to Arguments section below.

Response to Arguments

9. Applicant's arguments filed June 6, 2005 have been fully considered but they are not persuasive.

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Applicant asserts that a case of *prima facie* obviousness has not been established by the examiner and that because no secondary art reference was supplied, that it would have not been obvious to a skilled artisan to use a protein which kills bacteria for use as an antibiotic in a mammal (Remarks p. 9, paragraphs 2-3). It is also asserted by Applicant that their elected protein, SEQ ID No: 8 and gene 44 as taught in the prior art reference of Wie et al., teaches away from SEQ ID No: 8 as being the optimum antimicrobial protein (see. P-10-11). The examiner respectfully disagrees with these assertions for the following reasons. First, in order to establish a case of *prima facie* obviousness the following is needed:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP 2143-2143.03 for decisions pertinent to each of these criteria.

Thus, in the general knowledge given to a skilled artisan in the current field, the Master's level microbiologist and/or M.D. would recognize the clear benefits of a protein that kills host bacteria such as *E. coli* and/or *B. subtilis* and that said protein would be invaluable as an antibiotic/antimicrobial medicament. I

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reasonable expectation of success would be expected in light of the significant results afforded by the over-expression of the e3 gene (gene 44, SEQ ID No: 8) in bacterium. This leads on to applicants assertion that the prior art of Wie et al. is riddled with ambiguity about the effectiveness when used alone, in acting as an antimicrobial protein. Applicant seems to have confused two things here. First, when gene 44 (SEQ ID No: 8) is cloned into a plasmid, and subsequently transformed into either *E. coli* or *B. subtilis* and the protein over expressed in said bacteria, there is no question that the profound and significant effects that SEQ ID No: 8 fate of said bacteria which is cell death. "When the e3 gene was expressed from an inducible promoter in uninfected cells of either *E. coli* or *B. subtilis*, it caused the inhibition of DNA, RNA and protein synthesis and; ultimately, cell death (Wie et al. J.Bacteriol. 1993. v. 175, pp7887-7900)." (page 7933, 1st column, 1st paragraph). Thus it is clear that SEQ ID No: 8 acts as an antimicrobial protein. What applicant seems to be wrongly asserting, however, is that when there is a knockout mutation of the e3/gene 44 when the entire SPO1 genome is used to inhibit said bacteria, that since this mutation has no significant effect on the level of bacterial inhibition (cell death) then it must mean that it is not the only protein or gene (out of the 12-24 other genes of SPO1) involved in bacterial take-over that leads to cell death. The examiner certainly concedes this point, and agrees with Applicant that indeed, gene3/gene 44 (SEQ ID No: 8) most likely is not the only protein involved host takeover and cell death. However, clearly that is not the point. The point is that when SEQ ID No: 8 is

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over expressed in *E. coli* or *B. subtilis* it leads to cell death. It may not happen quite as quickly as when all 12-24 genes are involved, but it clearly happens at a significant level. As further evidence to this fact, see Wei, Ph.D. thesis, Chapter 4, from which the Wie et al. 1994 reference was obviously a part of (and which inventor Dr. Stewart was the Ph.D. supervisor).

Finally applicant argues that the examiner must consider the issue of "critical long-felt but unsolved needs and failures by others" in determining the issue of obviousness under 35 U.S.C. 103. Specifically, the fact that applicant has described in the specification that their bacteriophage and its antimicrobial properties overcomes what other conventional antibiotics do not, that being the Herxheimer reaction (the release of harmful endotoxins from dead bacteria into the blood once the bacteria cell wall has been ruptured, thus not only killing the bacteria but also releasing said endotoxins). IF Applicant were actually claiming a bacteriophage in its method, the examiner might consider this argument. However, since what is being claimed is a method of inhibiting bacterial infection in a mammal by administering a *protein*, said argument is irrelevant because by administering a single protein not contained within a phage, will induce the same sort of Herxheimer reaction as other antibiotics.

New Objections and Rejections

Inventorship

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

It is unclear to the examiner Dr. A.Y. Shamoo's role in the inventorship of the claimed invention. Specifically, what role an X-ray crystallographer has in the overall understanding of the early, mid and late stages of antimicrobial bacterium at the time of filing of this application. It is noted that Dr. Shamoo is absent on all 28+ publications that Dr. Stewart has been involved with dealing with *B. subtilis* SPO1 genes. Recent publications detailing the interactions of SEQ ID No: 8 (gene 44), SEQ ID No: 14 (gene 50) and SEQ ID No: 15 (gene 51) have also omitted Dr. Shamoo (see Sampath poster abstracts cited on the IDS from March 25, 2004 as an example). Clarification is sought in this matter.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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12. Claims 11-15, 17-20 and 22-25 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sampath et al.

Sampath et al. teach that various genes from *B. subtilis* are involved in SPO1 host-takeover and that by observing the effects of various knock-out mutations on some of the genes* such as 38, 39 and 40; genes 44, 50 and 51; and genes 53, 54 and 55 it was possible to identify the genes and thus protein products identified in host-shutoff (e.g. inhibition of host DNA synthesis or RNA synthesis). Furthermore, the following is explained:

"Many of the genes (38/39, 41, 44, 45/46, 50/51, 52 and 56), were lethal when expressed in *E. coli* and/or *B. subtilis*, suggesting that new antibiotics might be based on their lethal mechanisms. The combination of genes 44, 50 and 51 killed more than 20 times as rapidly as any of the individual genes."

It is further taught that knockout mutations in single genes such as 40, 44, 50, 51 or 56 were not efficient in decreasing the inhibition of host transcription. Finally, the shutoff of DNA, RNA or protein synthesis by individual genes or by combinations such as 44, 50 and 52 were not as rapid as that of the SPO1 which expressed 24 genes in combination.

Thus, one of ordinary skill in the art would have been able to recognize the potential that these various proteins from SPO1 have for the use as antibiotics. First, because Sampath et al. suggest the use of genes such as 44 (SEQ ID No: 8), 50 and 51 (SEQ ID Nos: 14 and 15, respectively) as well as other single genes/proteins and

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combinations thereof, and second, because the results of the expression of individual and combinations of said genes/proteins in bacteria (such as *E. coli* and *B. subtilis*) show specifically that they are capable of killing said bacteria. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to, to use the proteins such SEQ ID No: 8 (which is gene 44), alone or in combination, in an antibacterial composition and to administer it to a mammal in order to inhibit bacterial infection because Sampath et al. suggest that SEQ ID No: 8/gene 44 is a potentially a viable antibiotic, and clearly a skilled artisan recognizes the definition and intended uses of antibiotics, which are administered to mammals and humans who have bacterial infections.

Conclusion

12. No claims is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Mayer, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 8.30am to 5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

* The genes listed by Sampath et al. are the same as those listed in Table 1, p. 8-9 of the specification and the corresponding SEQ ID No: of the expressed proteins: Thus, gene 38 = SEQ ID No: 2; gene 44 = SEQ ID No: 8; gene 50 = SEQ ID No: 14; gene 51 = SEQ ID No: 15.

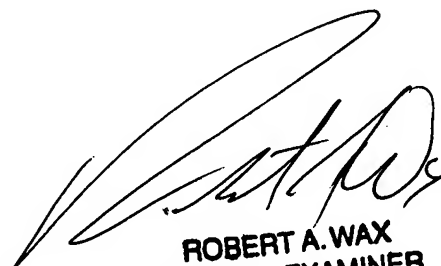
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SMM

29 August 2005



ROBERT A. WAX
PRIMARY EXAMINER